CombiGlide 1.0

Quick Start Guide

Schrödinger Press

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Document Conventions

In addition to the use of italics for names of documents, the font conventions that are used in this document are summarized in the table below.

Table 3.1.

Font	Example	Use
Sans serif	Project Table	Names of GUI features, such as panels, menus, menu items, buttons, and labels
Monospace	`$SCHRODINGER/maestro`	File names, directory names, commands, environment variables, and screen output
Italic	*filename*	Text that the user must replace with a value
Sans serif uppercase	CTRL+H	Keyboard keys

In descriptions of command syntax, the following UNIX conventions are used: braces `{ }` enclose a choice of required items, square brackets `[ ]` enclose optional items, and the bar symbol | separates items in a list from which one item must be chosen. Lines of command syntax that wrap should be interpreted as a single command.

In this document, to *type* text means to type the required text in the specified location, and to *enter* text means to type the required text, then press the ENTER key.

References to literature sources are given in square brackets, like this: [10].

Overview

1.1 About CombiGlide

CombiGlide™ is a tool for the rapid virtual screening of combinatorial libraries to eliminate unpromising compounds beforehand. The CombiGlide process uses the extra precision (XP) mode of our docking program, Glide™. The centerpiece of the approach is a proprietary selection protocol that rapidly determines which members of the virtual library have the highest likelihood of binding well to the target. These compounds are then enumerated and docked. A variety of library selection strategies is provided, including methods for the incorporation of predicted ADME properties into the overall decision process. CombiGlide can be used in the lead discovery or lead optimization phases of a program. In the lead discovery phase, various cores, sites of diversity, and chemistries can be evaluated. In the lead optimization phase, the importance of functionality at different positions on the initial hit can be evaluated along with screening extensive collections of side chains at each position. Thus, CombiGlide provides a flexible structure-based method for determining optimal focused combinatorial libraries.

1.2 About this Document

This document provides tutorial instruction in the use of CombiGlide to design a focused library.

- Chapter 2 provides an overview of the basic capabilities of Maestro, the graphical user interface (GUI) for all Schrödinger products. For more information on Maestro, see the Maestro online help, the *Maestro User Manual*, or the *Maestro Tutorial*.
- Chapter 3 contains exercises on focused library design.
- Chapter 4 provides information on how to get help if you encounter any problems.

Introduction to Maestro

Maestro is the graphical user interface for all of Schrödinger's products: CombiGlide™, Epik™, Glide™, Impact™, Jaguar™, Liaison™, LigPrep™, MacroModel®, Phase™, Prime™, QikProp™, QSite™, SiteMap™, and Strike™. It contains tools for building, displaying, and manipulating chemical structures; for organizing, loading, and storing these structures and associated data; and for setting up, monitoring, and visualizing the results of calculations on these structures. This chapter provides a brief introduction to Maestro and some of its capabilities. For more information on any of the topics in this chapter, see the *Maestro User Manual*.

2.1 General Interface Behavior

Most Maestro panels are amodal: more than one panel can be open at a time, and a panel need not be closed for an action to be carried out. Each Maestro panel has a Close button so you can hide the panel from view.

Maestro supports the mouse functions common to many graphical user interfaces. The left button is used for choosing menu items, clicking buttons, and selecting objects by clicking or dragging. This button is also used for resizing and moving panels. The right button displays a shortcut menu. Other common mouse functions are supported, such as using the mouse in combination with the SHIFT or CTRL keys to select a range of items and select or deselect a single item without affecting other items.

In addition, the mouse buttons are used for special functions described later in this chapter. These functions assume that you have a three-button mouse. If you have a two-button mouse, ensure that it is configured for three-button mouse simulation (the middle mouse button is simulated by pressing or holding down both buttons simultaneously).

2.2 Starting Maestro

Before starting Maestro, you must first set the `SCHRODINGER` environment variable to point to the installation directory. To set this variable, enter the following command at a shell prompt:

csh/tcsh: `setenv SCHRODINGER` *installation-directory*

bash/ksh: `export SCHRODINGER=`*installation-directory*

You might also need to set the DISPLAY environment variable, if it is not set automatically when you log in. To determine if you need to set this variable, enter the command:

```
echo $DISPLAY
```

If the response is a blank line, set the variable by entering the following command:

csh/tcsh: `setenv DISPLAY` *display-machine-name*`:0.0`

bash/ksh: `export DISPLAY=`*display-machine-name*`:0.0`

After you set the SCHRODINGER and DISPLAY environment variables, you can start Maestro using the command:

```
$SCHRODINGER/maestro options
```

If you add the $SCHRODINGER directory to your path, you only need to enter the command maestro. Options for this command are given in Section 2.1 of the *Maestro User Manual*.

The directory from which you started Maestro is Maestro's current working directory, and all data files are written to and read from this directory unless otherwise specified (see Section 2.8 on page 25). You can change directories by entering the following command in the command input area (see page 6) of the main window:

```
cd directory-name
```

where *directory-name* is either a full path or a relative path.

2.3 The Maestro Main Window

The Maestro main window is shown in Figure 2.1 on page 5. The main window components are listed below.

The following components are always visible:

- **Title bar**—displays the Maestro version, the project name (if there is one) and the current working directory.
- **Auto-Help**—automatically displays context-sensitive help.
- **Menu bar**—provides access to panels.
- **Workspace**—displays molecular structures and other 3D graphical objects.

The following components can be displayed or hidden by choosing the component from the Display menu. Your choice of which main window components are displayed is persistent between Maestro sessions.

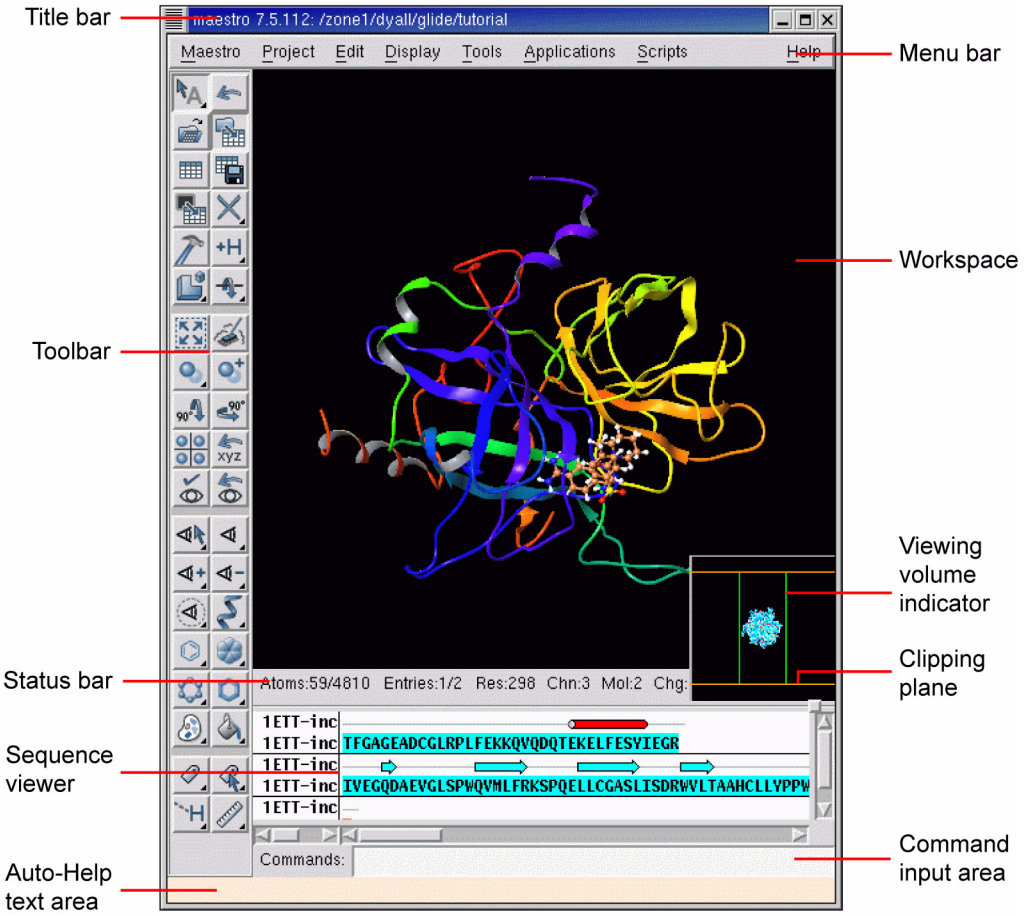

Figure 2.1. The Maestro main window.

- **Toolbar**—contains buttons for many common tasks and provides tools for displaying and manipulating structures, as well as organizing the Workspace.
- **Status bar**—displays information about a particular atom, or about structures in the Workspace, depending on where the pointer pauses (see Section 2.5 of the *Maestro User Manual* for details):
  - **Atom**—displays the chain, residue number, element, PDB atom name, formal charge, and title or entry name (this last field is set by choosing Preferences from the Maestro menu and selecting the Feedback folder).
  - **Workspace**—displays the number of atoms, entries, residues, chains, and molecules in the Workspace.

- **Clipping planes window**—displays a small, top view of the Workspace and shows the clipping planes and viewing volume indicators.
- **Sequence viewer**—shows the sequences for proteins displayed in the Workspace. See Section 2.6 of the *Maestro User Manual* for details.
- **Command input area**—provides a place to enter Maestro commands.

When a distinction between components in the main window and those in other panels is needed, the term *main* is applied to the main window components (e.g., main toolbar).

You can expand the Workspace to occupy the full screen, by pressing CTRL+=. All other components and panels are hidden. To return to the previous display, press CTRL+= again.

2.3.1 The Menu Bar

The menus on the main menu bar provide access to panels, allow you to execute commands, and control the appearance of the Workspace. The main menus are as follows:

- Maestro—save or print images in the Workspace, execute system commands, save or load a panel layout, set preferences, set up Maestro command aliases, and quit Maestro.
- Project—open and close projects, import and export structures, make a snapshot, and annotate a project. These actions can also be performed from the Project Table panel. For more information, see Section 2.4 on page 11.
- Edit—undo actions, build and modify structures, define command scripts and macros, and find atoms in the Workspace.
- Display—control the display of the contents of the Workspace, arrange panels, and display or hide main window components.
- Tools—group atoms; measure, align, and superimpose structures; and view and visualize data.
- Applications—set up, submit, and monitor jobs for Schrödinger's computational programs. Some products have a submenu from which you can choose the task to be performed.
- Scripts—manage and install Python scripts that come with the distribution and scripts that you create yourself. (See Chapter 13 of the *Maestro User Manual* for details.)
- Help—open the Help panel, the PDF documentation index, or information panels; run a demonstration; and display or hide Balloon Help (tooltips).

2.3.2 The Toolbar

The main toolbar contains three kinds of buttons for performing common tasks:

Action—Perform a simple task, like clearing the Workspace.

Display—Open or close a panel or open a dialog box, such as the Project Table panel.

Menu—Display a *button menu*. These buttons have a triangle in the lower right corner.

There are four types of items on button menus, and all four types can be on the same menu (see Figure 2.2):

- **Action**—Perform an action immediately.
- **Display**—Open a panel or dialog box.
- **Object types for selection**—Choose Atoms, Bonds, Residues, Chains, Molecules, or Entries, then click on an atom in the Workspace to perform the action on all the atoms in that structural unit.

  The object type is marked on the menu with a red diamond and the button is indented to indicate the action to be performed.
- **Other setting**—Set a state, choose an attribute, or choose a parameter and click on atoms in the Workspace to display or change that parameter.

The toolbar buttons are described below. Some descriptions refer to features not described in this chapter. See the *Maestro User Manual* for a fuller description of these features.

Figure 2.2. The Workspace selection ***button menu and the*** Adjust distances, angles or dihedrals ***button menu.***

Workspace selection
– Choose an object type for selecting
– Open the Atom Selection dialog box

Undo/Redo
Undo or redo the last action. Performs the same function as the Undo item on the Edit menu, and changes to an arrow pointing in the opposite direction when an Undo has been performed, indicating that its next action is Redo.

Open a project
Open the Open Project dialog box.

Import structures
Open the Import panel.

Open/Close Project Table
Open the Project Table panel or close it if it is open.

Save as
Open the Save Project As dialog box, to save the project with a new name.

Create entry from Workspace
Open a dialog box in which you can create an entry in the current project using the contents of the Workspace.

Delete
– Choose an object type for deletion
– Delete hydrogens and waters
– Open the Atom Selection dialog box
– Delete other items associated with the structures in the Workspace
– Click to select atoms to delete
– Double-click to delete all atoms

Open/Close Build panel
Open the Build panel or close it if it is open.

Add hydrogens
– Choose an object type for applying a hydrogen treatment
– Open the Atom Selection dialog box
– Click to select atoms to treat
– Double-click to apply to all atoms

Local transformation
– Choose an object type for transforming
– Click to select atoms to transform
– Open the Advanced Transformations panel

Adjust distances, angles or dihedrals
– Choose a parameter for adjusting
– Delete adjustments

Fit to screen
Scale the displayed structure to fit into the Workspace and reset the center of rotation.

Clear Workspace
Clear all atoms from the Workspace.

Set fog display state
Choose a fog state. Automatic means fog is on when there are more than 40 atoms in the Workspace, otherwise it is off.

Enhance depth cues
Optimize fogging and other depth cues based on what is in the Workspace.

Rotate around X axis by 90 degrees
Rotate the Workspace contents around the X axis by 90 degrees.

Rotate around Y axis by 90 degrees
Rotate the Workspace contents around the Y axis by 90 degrees.

Tile entries
Arrange entries in a rectangular grid in the Workspace.

Reset Workspace
Reset the rotation, translation, and zoom of the Workspace to the default state.

Save view
Save the current view of the Workspace: orientation, location, and zoom.

Restore view
Restore the last saved view of the Workspace: orientation, location, and zoom.

Display only selected atoms
– Choose an object type for displaying
– Click to select atoms to display
– Double-click to display all atoms

Display only
– Choose a predefined atom category
– Open the Atom Selection dialog box

Also display
– Choose a predefined atom category
– Open the Atom Selection dialog box

Undisplay
– Choose a predefined atom category
– Open the Atom Selection dialog box

Display residues within N angstroms of currently displayed atoms
– Choose a radius
– Open a dialog box to set a value

Show, hide, or color ribbons
– Choose to show or hide ribbons
– Choose a color scheme for coloring ribbons

Draw bonds in wire
– Choose an object type for drawing bonds in wire representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

Draw atoms in CPK
– Choose an object type for drawing bonds in CPK representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

Draw atoms in Ball & Stick
– Choose an object type for drawing bonds in Ball & Stick representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

Draw bonds in tube
– Choose an object type for drawing bonds in tube representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

Color all atoms by scheme
Choose a predefined color scheme.

Color residue by constant color
– Choose a color for applying to residues
– Click to select residues to color
– Double-click to color all atoms

Label atoms
– Choose a predefined label type
– Delete labels

Label picked atoms
– Choose an object type for labeling atoms
– Open the Atom Selection dialog box
– Open the Atom Labels panel at the Composition folder
– Delete labels
– Click to select atoms to label
– Double-click to label all atoms

Display H-bonds
– Choose bond type:
intra—displays H-bonds within the selected molecule
inter—displays H-bonds between the selected molecule and all other atoms.
– Delete H-bonds
– Click to select molecule

Measure distances, angles or dihedrals
– Choose a parameter for displaying measurements
– Delete measurements
– Click to select atoms for measurement

2.3.3 Mouse Functions in the Workspace

The left mouse button is used for selecting objects. You can either click on a single atom or bond, or you can drag to select multiple objects. The right mouse button opens shortcut menus, which are described in Section 2.7 of the *Maestro User Manual*.

The middle and right mouse buttons can be used on their own and in combination with the SHIFT and CTRL keys to perform common operations, such as rotating, translating, centering, adjusting, and zooming.

Table 2.1. Mapping of Workspace operations to mouse actions.

Mouse Button	Keyboard	Motion	Action
Left		click, drag	Select
Left	SHIFT	click, drag	Toggle the selection
Middle		drag	Rotate about X and Y axes Adjust bond, angle, or dihedral
Middle	SHIFT	drag vertically	Rotate about X axis
Middle	SHIFT	drag horizontally	Rotate about Y axis
Middle	CTRL	drag horizontally	Rotate about Z axis
Middle	SHIFT + CTRL	drag horizontally	Zoom
Right		click	Spot-center on selection
Right		click and hold	Display shortcut menu
Right		drag	Translate in the X-Y plane
Right	SHIFT	drag vertically	Translate along the X axis
Right	SHIFT	drag horizontally	Translate along the Y axis
Right	CTRL	drag horizontally	Translate along the Z axis
Middle & Right		drag horizontally	Zoom

2.3.4 Shortcut Key Combinations

Some frequently used operations have been assigned shortcut key combinations. The shortcuts available in the main window are described in Table 2.2.

Table 2.2. Shortcut keys in the Maestro main window.

Keys	Action	Equivalent Menu Choices
CTRL+B	Open Build panel	Edit > Build
CTRL+C	Create entry	Project > Create Entry From Workspace
CTRL+E	Open Command Script Editor panel	Edit > Command Script Editor
CTRL+F	Open Find Atoms panel	Edit > Find
CTRL+H	Open Help panel	Help > Help
CTRL+I	Open Import panel	Project > Import Structures
CTRL+M	Open Measurements panel	Tools > Measurements
CTRL+N	Create new project	Project > New
CTRL+O	Open project	Project > Open
CTRL+P	Print	Maestro > Print
CTRL+Q	Quit	Maestro > Quit
CTRL+S	Open Sets panel	Tools > Sets
CTRL+T	Open Project Table panel	Project > Show Table
CTRL+W	Close project	Project > Close
CTRL+Z	Undo/Redo last command	Edit > Undo/Redo
CTRL+=	Enter and exit full screen mode (Workspace occupies full screen)	None

2.4 Maestro Projects

All the work you do in Maestro is done within a *project*. A project consists of a set of *entries*, each of which contains one or more chemical structures and their associated data. In any Maestro session, there can be only one Maestro project open. If you do not specify a project when you start Maestro, a *scratch* project is created. You can work in a scratch project without saving it, but you must save it in order to use it in future sessions. When you save or close a project, all the view transformations (rotation, translation, and zoom) are saved with it. When you close a project, a new scratch project is automatically created.

Likewise, if there is no entry displayed in the Workspace, Maestro creates a *scratch* entry. Structures that you build in the Workspace constitute a scratch entry until you save the structures as project entries. The scratch entry is not saved with the project unless you explicitly add it to the project. However, you can use a scratch entry as input for some calculations.

To add a scratch entry to a project, do one of the following:

- Click the Create entry from Workspace button:

- Choose Create Entry from Workspace from the Project menu.
- Press CTRL+C.

In the dialog box, enter a name and a title for the entry. The entry name is used internally to identify the entry and can be modified by Maestro. The title can be set or changed by the user, but is not otherwise modified by Maestro.

Once an entry has been incorporated into the project, its structures and their data are represented by a row in the Project Table. Each row contains the row number, an icon indicating whether the entry is displayed in the Workspace (the In column), the entry title, a button to open the Surfaces panel if the entry has surfaces, the entry name, and any entry properties. The row number is not a property of the entry.

Entries can be collected into groups, and the members of the group can be displayed or hidden. Most additions of multiple entries to the Project Table are done as entry groups.

You can use entries as input for all of the computational programs—Glide, Impact, Jaguar, Liaison, LigPrep, MacroModel, Phase, Prime, QikProp, QSite, and Strike. You can select entries as input for the ePlayer, which displays the selected structures in sequence. You can also duplicate, combine, rename, and sort entries; create properties; import structures as entries; and export structures and properties from entries in various formats.

To open the Project Table panel, do one of the following:

- Click the Open/Close Project Table button on the toolbar

- Choose Show Table from the Project menu
- Press CTRL+T.

The Project Table panel contains a menu bar, a toolbar, and the table itself.

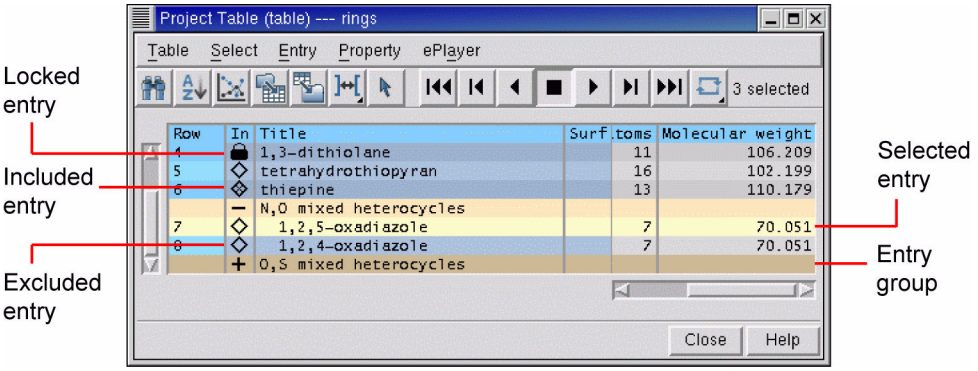

Figure 2.3. The** Project Table **panel.

2.4.1 The Project Table Toolbar

The Project Table toolbar contains two groups of buttons and a status display. The first set of buttons opens various panels that allow you to perform functions on the entries in the Project Table. The second set of buttons controls the ePlayer, which "plays through" the selected structures: each structure is displayed in the Workspace in sequence, at a given time interval. See Section 2.3.2 on page 7 for a description of the types of toolbar buttons. The buttons are described below.

Find
Open the Find panel for locating alphanumeric text in any column of the Project Table, except for the row number.

Sort
Open the Sort panel for sorting entries by up to three properties.

Plot
Open the Plot panel for plotting entry properties.

Import Structure
Open the Import panel for importing structures into the project.

Export Structure
Open the Export panel for exporting structures to a file.

Columns
Choose an option for adjusting the column widths.

Select only
Open the Entry Selection dialog box for selecting entries based on criteria for entry properties.

Go to start
Display the first selected structure.

Previous
Display the previous structure in the list of selected structures.

Play backward
Display the selected structures in sequence, moving toward the first.

Stop
Stop the ePlayer.

Play forward
Display the selected structures in sequence, moving toward the last.

Next
Display the next structure in the list of selected structures.

Go to end
Display the last selected structure.

Loop
Choose an option for repeating the display of the structures. Single Direction displays structures in a single direction, then repeats. Oscillate reverses direction each time the beginning or end of the list is reached.

The status display, to the right of the toolbar buttons, shows the number of selected entries. When you pause the cursor over the status display, the Balloon Help shows the total number of entries, the number shown in the table, the number selected, and the number included in the Workspace.

2.4.2 The Project Table Menus

- Table—find text, sort entries, plot properties, import and export structures, and configure the Project Table.
- Select—select all entries, none, invert your selection, or select classes of entries using the Entry Selection dialog box and the Filter panel.
- Entry—include or exclude entries from the Workspace, display or hide entries in the Project Table, and perform various operations on the selected entries.
- Property—display and manipulate entry properties in the Project Table.
- ePlayer—view entries in succession, stop, reverse, and set the ePlayer options.

2.4.3 Selecting Entries

Many operations in Maestro are performed on the entries selected in the Project Table. The Project Table functions much like any other table: select rows by clicking, shift-clicking, and control-clicking. However, because clicking in an editable cell of a selected row enters edit mode, you should click in the Row column to select entries. See Section 2.4.5 on page 16 for more information on mouse actions in the Project Table. There are shortcuts for selecting classes of entries on the Select menu.

In addition to selecting entries manually, you can select entries that meet a combination of conditions on their properties. Such combinations of conditions are called *filters*. Filters are Entry Selection Language (ESL) expressions and are evaluated at the time they are applied. For example, if you want to set up a Glide job that uses ligands with a low molecular weight (say, less than 300) and that has certain QikProp properties, you can set up a filter and use it to select entries for the job. If you save the filter, you can use it again on a different set of ligands that meet the same selection criteria.

To create a filter:

1. Do one of the following:
   - Choose Only, Add, or Deselect from the Select menu.
   - Click the Entry selection button on the toolbar.

   
2. In the Properties folder, select a property from the property list, then select a condition.
3. Combine this selection with the current filter by clicking Add, Subtract, or Intersect. These buttons perform the Boolean operations OR, AND NOT, and AND on the corresponding ESL expressions.
4. To save the filter for future use click Create Filter, enter a name, and click OK.
5. Click OK to apply the filter immediately.

2.4.4 Including Entries in the Workspace

In addition to selecting entries, you can also use the Project Table to control which entries are displayed in the Workspace. An entry that is displayed in the Workspace is *included* in the Workspace; likewise, an entry that is not displayed is *excluded*. Included entries are marked by an X in the diamond in the In column; excluded entries are marked by an empty diamond. Entry inclusion is completely independent of entry selection.

To include or exclude entries, click, shift-click, or control-click in the In column of the entries, or select entries and choose Include or Exclude from the Entry menu. Inclusion with the mouse works just like selection: when you include an entry by clicking, all other entries are excluded.

It is sometimes useful to keep one entry in the Workspace and include others one by one: for example, a receptor and a set of ligands. You can fix the receptor in the Workspace by selecting it in the Project Table and choosing Fix from the Entry menu or by pressing CTRL+F. A padlock icon replaces the diamond in the In column to denote a *fixed* entry. To remove a fixed entry from the Workspace, you must exclude it explicitly (CTRL+X). It is not affected by the inclusion or exclusion of other entries. Fixing an entry affects only its inclusion; you can still rotate, translate, or modify the structure.

2.4.5 Mouse Functions in the Project Table

The Project Table supports the standard use of shift-click and control-click to select objects. This behavior applies to the selection of entries and the inclusion of entries in the Workspace. You can also drag to resize rows and columns and to move rows.

You can drag a set of non-contiguous entries to reposition them in the Project Table. When you release the mouse button, the entries are placed after the first unselected entry that precedes the entry on which the cursor is resting. For example, if you select entries 2, 4, and 6, and release the mouse button on entry 3, these three entries are placed after entry 1, because entry 1 is the first unselected entry that precedes entry 3. To move entries to the top of the table, drag them above the top of the table; to move entries to the end of the table, drag them below the end of the table.

A summary of mouse functions in the Project Table is provided in Table 2.3.

Table 2.3. Mouse operations in the Project Table.

Task	Mouse Operation
Change a Boolean property value	Click repeatedly in a cell to cycle through the possible values (On, Off, Clear)
Display the Entry menu for an entry	Right-click anywhere in the entry. If the entry is not selected, it becomes the selected entry. If the entry is selected, the action is applied to all selected entries.
Display a version of the Property menu for a property	Right-click in the column header
Edit the text or the value in a table cell	Click in the cell and edit the text or value
Include an entry in the Workspace, exclude all others	Click the In column of the entry

Table 2.3. Mouse operations in the Project Table. (Continued)

Task	Mouse Operation
Move selected entries	Drag the entries
Paste text into a table cell	Middle-click
Resize rows or columns	Drag the boundary with the middle mouse button
Select an entry, deselect all others	For an unselected entry, click anywhere in the row except the In column; for a selected entry, click the row number.
Select or include multiple entries	Click the first entry then shift-click the last entry
Toggle the selection or inclusion state	Control-click the entry or the In column

2.4.6 Project Table Shortcut Keys

Some frequently used project operations have been assigned shortcut key combinations. The shortcuts, their functions, and their menu equivalents are listed in Table 2.4.

Table 2.4. Shortcut keys in the Project Table.

Keys	Action	Equivalent Menu Choices
CTRL+A	Select all entries	Select > All
CTRL+F	Fix entry in Workspace	Entry > Fix
CTRL+I	Open Import panel	Table > Import Structures
CTRL+N	Include only selected entries	Entry > Include Only
CTRL+U	Deselect all entries	Select > None
CTRL+X	Exclude selected entries	Entry > Exclude
CTRL+Z	Undo/Redo last command	Edit > Undo/Redo in main window

2.5 Building a Structure

After you start Maestro, the first task is usually to create or import a structure. You can open existing Maestro projects or import structures from other sources to obtain a structure, or you can build your own. To open the Build panel, do one of the following:

- Click the Open/Close Build panel button in the toolbar:

- Choose Build from the Edit menu.
- Press CTRL+B.

The Build panel allows you to create structures by drawing or placing atoms or fragments in the Workspace and connecting them into a larger structure, to adjust atom positions and bond orders, and to change atom properties. This panel contains a toolbar and three folders.

2.5.1 Placing and Connecting Fragments

The Build panel provides several tools for creating structures in the Workspace. You can place and connect fragments, or you can draw a structure freehand.

To place a fragment in the Workspace:

1. Select Place.
2. Choose a fragment library from the Fragments menu.
3. Click a fragment.
4. Click in the Workspace where you want the fragment to be placed.

To connect fragments in the Workspace, do one of the following:

- Place another fragment and connect them using the Connect & Fuse panel, which you open from the Edit menu on the main menu bar or with the Display Connect & Fuse panel on the Build toolbar.

- Replace one or more atoms in the existing fragment with another fragment by selecting a fragment and clicking in the Workspace on the main atom to be replaced.
- Grow another fragment by selecting Grow in the Build panel and clicking the fragment you want to add in the Fragments folder.

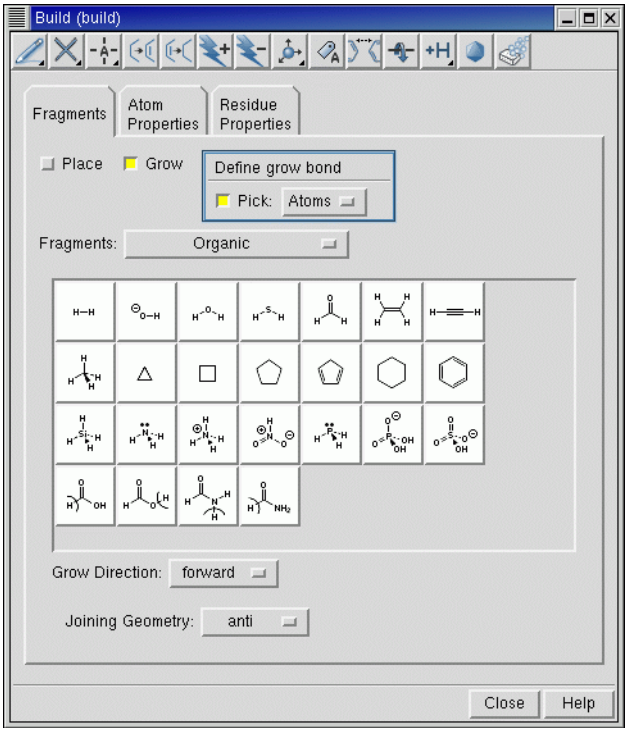

Figure 2.4. The* Build *panel.

Grow mode uses predefined rules to connect a fragment to the *grow bond*. The grow bond is marked by a green arrow. The new fragment replaces the atom at the head of the arrow on the grow bond and all atoms attached to it. To change the grow bond, choose Bonds from the Pick option menu in the Build panel and click on the desired grow bond in the Workspace. The arrow points to the atom nearest to where you clicked.

To draw a structure freehand:

1. Choose an element from the Draw button menu on the Build panel toolbar:

2. Click in the Workspace to place an atom of that element.
3. Click again to place another atom and connect it to the previous atom.
4. Continue this process until you have drawn the structure.
5. Click the active atom again to finish drawing.

2.5.2 Adjusting Properties

In the Atom Properties folder, you can change the properties of the atoms in the Workspace. For each item on the Property option menu—Element, Atom Type (MacroModel), Partial Charge, PDB Atom Name, Grow Name, and Atom Name—there is a set of tools you can use to change the atom properties. For example, the Element tools consist of a periodic table from which you can choose an element and select an atom to change it to an atom of the selected element.

Similarly, the Residue Properties folder provides tools for changing the properties of residues: the Residue Number, the Residue Name, and the Chain Name.

To adjust bond lengths, bond angles, dihedral angles, and chiralities during or after building a structure, use the Adjust distances, angles or dihedrals button on the main toolbar:

You can also open the Adjust panel from this button menu, from the Display Adjust panel button on the Build panel toolbar (which has the same appearance as the above button) or from the Edit menu in the main window.

2.5.3 The Build Panel Toolbar

The toolbar of the Build panel provides quick access to tools for drawing and modifying structures and labeling atoms. See Section 2.3.2 on page 7 for a description of the types of toolbar buttons. The toolbar buttons and their use are described below.

Free-hand drawing
Choose an element for drawing structures freehand in the Workspace (default C). Each click in the Workspace places an atom and connects it to the previous atom.

Delete
Choose an object for deleting. Same as the Delete button on the main toolbar, see page 8.

Set element
Choose an element for changing atoms in the Workspace (default C). Click an atom to change it to the selected element.

Increment bond order
Select a bond to increase its bond order by one, to a maximum of 3.

Decrement bond order
Select a bond to decrease its bond order by one, to a minimum of 0.

Increment formal charge
Select an atom to increase its formal charge by one.

Decrement formal charge
Select an atom to decrease its formal charge by one.

Move
Choose a direction for moving atoms, then click the atom to be moved. Moves in the XY plane are made by clicking the new location. Moves in the Z direction are made in 0.5 Å increments.

Label
Apply heteroatom labels as you build a structure. The label consists of the element name and formal charge, and is applied to atoms other than C and H.

Display Connect & Fuse panel
Open the Connect & Fuse panel so you can connect structures (create bonds between structures) or fuse structures (replace atoms of one structure with those of another).

Display Adjust panel
Open the Adjust panel so you can change bond lengths, bond angles, dihedral angles, or atom chiralities.

Add hydrogens
Choose an atom type for applying the current hydrogen treatment. Same as the Add hydrogens button on the main toolbar, see page 8.

Geometry Symmetrizer
Open the Geometry Symmetrizer panel for symmetrizing the geometry of the structure in the Workspace.

Geometry Cleanup
Clean up the geometry of the structure in the Workspace.

2.6 Selecting Atoms

Maestro has a powerful set of tools for selecting atoms in a structure: toolbar buttons, picking tools in panels, and the Atom Selection dialog box. These tools allow you to select atoms in two ways:

- Select atoms first and apply an action to them
- Choose an action first and then select atoms for that action

2.6.1 Toolbar Buttons

The small triangle in the lower right corner of a toolbar button indicates that the button contains a menu. Many of these buttons allow you to choose an object type for selecting: choose Atoms, Bonds, Residues, Chains, Molecules, or Entries, then click on an atom in the Workspace to perform the action on all the atoms in that structural unit.

For example, to select atoms with the Workspace selection toolbar button:

1. Choose Residues from the Workspace selection button menu:

   

   The button changes to:

   

2. Click on an atom in a residue in the Workspace to select all the atoms in that residue.

2.6.2 Picking Tools

The picking tools are embedded in each panel in which you need to select atoms to apply an operation. The picking tools in a panel can include one or more of the following:

- Pick option menu—Allows you to choose an object type. Depending on the operation to be performed, you can choose Atoms, Bonds, Residues, Chains, Molecules, or Entries, then click on an atom in the Workspace to perform the action on all the atoms in that structural unit.

  The Pick option menu varies from panel to panel, because not all object types are appropriate for a given operation. For example, some panels have only Atoms and Bonds in the Pick option menu.

- All button—Performs the action on all atoms in the Workspace.
- Selection button—Performs the action on any atoms already selected in the Workspace.
- Previous button—Performs the action on the most recent atom selection defined in the Atom Selection dialog box.
- Select button—Opens the Atom Selection dialog box.
- ASL text box—Allows you to type in an ASL expression for selecting atoms.

  ASL stands for Atom Specification Language, and is described in detail in the *Maestro Command Reference Manual*.

- Clear button—Clears the current selection

  

- Show markers option—Marks the selected atoms in the Workspace.

For example, to label atoms with the Label Atoms panel:

1. Choose Atom Labels from the Display menu.
2. In the Composition folder, select Element and Atom Number.
3. In the picking tools section at the top of the panel, you could do one of the following:
   - Click Selection to apply labels to the atoms already selected in the Workspace (from the previous example).
   - Choose Residues from the Pick option menu and click on an atom in a different residue to label all the atoms in that residue.

2.6.3 The Atom Selection Dialog Box

If you wish to select atoms based on more complex criteria, you can use the Atom Selection dialog box. To open this dialog box, choose Select from a button menu or click the Select button in a panel. See Section 5.3 of the *Maestro User Manual* for detailed instructions on how to use the Atom Selection dialog box.

2.7 Scripting in Maestro

Although you can perform nearly all Maestro-supported operations through menus and panels, you can also perform operations using Maestro commands, or compilations of these commands, called *scripts*. Scripts can be used to automate lengthy procedures or repetitive tasks and can be created in several ways. These are summarized below.

2.7.1 Python Scripts

Python is a full-featured scripting language that has been embedded in Maestro to extend its scripting facilities. The Python capabilities within Maestro include access to Maestro functionality for dealing with chemical structures, projects, and Maestro files.

The two main Python commands used in Maestro are:

- `pythonrun`—executes a Python module. (You can also use the alias `pyrun`.) The syntax is:

  `pythonrun` *module*`.`*function*

- `pythonimport`—rereads a Python file so that the next time you use the `pythonrun` command, it uses the updated version of the module. (You can also use the alias `pyimp`.)

From the Maestro Scripts menu you can install, manage, and run Python scripts. For more information on the Scripts menu, see Section 13.1 of the *Maestro User Manual*.

For more information on using Python with Maestro, see *Scripting with Python*.

2.7.2 Command Scripts

All Maestro commands are logged and displayed in the Command Script Editor panel. This means you can create a command script by performing the operations with the GUI controls, copying the logged commands from the Command History list into the Script text area of the panel, then saving the list of copied commands as a script.

To run an existing command script:

1. Open the Command Script Editor panel from the Edit menu in the main window.
2. Click Open Local and navigate to the directory containing the desired script.
3. Select a script in the Files list and click Open.

   The script is loaded into the Script window of the Command Script Editor panel.
4. Click Run Script.

Command scripts cannot be used for Prime operations.

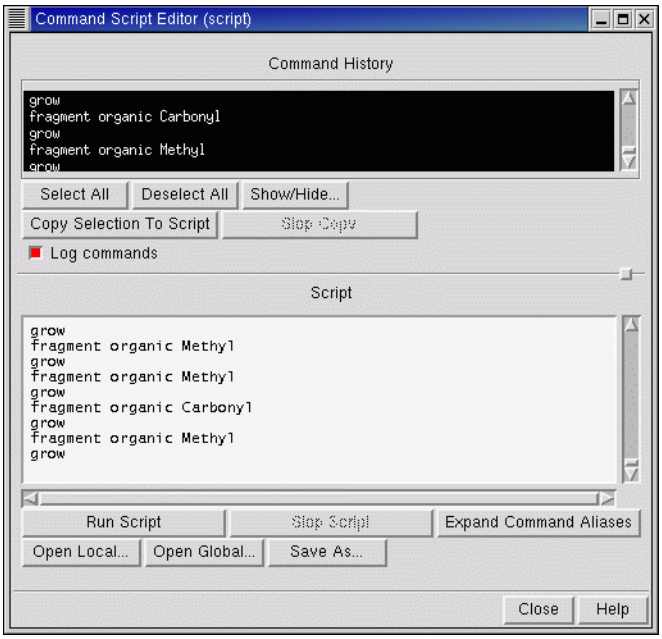

Figure 2.5. The** Command Script Editor **panel.

2.7.3 Macros

There are two kinds of macros you can create: named macros and macros assigned to function keys F1 through F12.

To create and run a named macro:

1. Open the Macros panel from the Edit menu in the main window.
2. Click New, enter a name for the macro, and click OK.
3. In the Definition text box, type the commands for the macro.
4. Click Update to update the macro definition.
5. To run the macro, enter the following in the command input area in the main window:

   `macrorun` *macro-name*

   If the command input area is not visible, choose Command Input Area from the Display menu.

To create and run a function key macro:

1. Open the Function Key Macros panel from the Edit menu in the main window.
2. From the Macro Key option, select a function key (F1 through F12) to which to assign the macro.
3. In the text box, type the commands for the macro.
4. Click Run to test the macro or click Save to save it.
5. To run the macro from the main window, press the assigned function key.

For more information on macros, see Section 13.5 of the *Maestro User Manual*.

2.8 Specifying a Maestro Working Directory

When you use Maestro to launch CombiGlide jobs, Maestro writes job output to the directory specified in the Directory folder of the Preferences panel. By default, this directory (the file I/O directory) is the directory from which you started Maestro.

To change the Maestro working directory:

1. Open the Preferences panel from the Maestro menu.
2. Click the Directory tab.
3. Select the directory you want to use for reading and writing files.

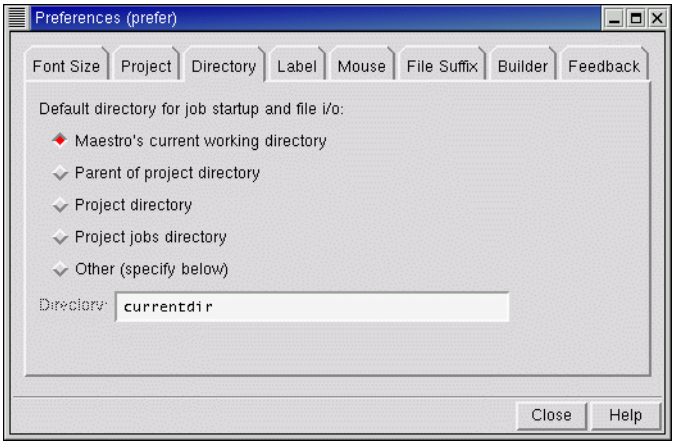

Figure 2.6. The** Directory **folder of the** Preferences **panel.

You can also set other preferences in the Preferences panel. See Section 12.2 of the *Maestro User Manual* for details.

2.9 Undoing an Operation

To undo a single operation, click the Undo button in the toolbar, choose Undo from the Edit menu, or press CTRL+Z. The word Undo in the menu is followed by text that describes the operation to undo. Not all operations can be undone: for example, global rotations and translations are not undoable operations. For such operations you can use the Save view and Restore view buttons in the toolbar, which save and restore a molecular orientation.

2.10 Running and Monitoring Jobs

Maestro has panels for each product for preparing and submitting jobs. To use these panels, choose the appropriate product and task from the Applications menu and its submenus. Set the appropriate options in the panel, then click Start to open the Start dialog box and set options for running the job. For a complete description of the Start dialog box associated with your computational program, see your product's User Manual. When you have finished setting the options, click Start to launch the job and open the Monitor panel.

The Monitor panel is the control panel for monitoring the progress of jobs and for pausing, resuming, or killing jobs. All jobs that belong to you can be displayed in the Monitor panel, whether or not they were started from Maestro. Subjobs are indented under their parent in the job list. The text pane shows output information from the monitored job, such as the contents

of the log file. The Monitor panel opens automatically when you start a job. If it is not open, you can open it by choosing Monitor from the Applications menu in the Maestro main window.

While jobs are running, the Detach, Pause, Resume, Stop, Kill, and Update buttons are active. When there are no jobs currently running, only the Monitor and Delete buttons are active. These buttons act on the selected job. By default, only jobs started from the current project are shown. To show other jobs, deselect Show jobs from current project only.

When a monitored job ends, the results are incorporated into the project according to the settings used to launch the job. If a job that is not currently being monitored ends, you can select it in the Monitor panel and click Monitor to incorporate the results. Monitored jobs are incorporated only if they are part of the current project. You can monitor jobs that are not part of the current project, but their results are not incorporated. To add their results to a project, you must open the project and import the results.

Further information on job control, including configuring your site, monitoring jobs, running jobs, and job incorporation, can be found in the *Job Control Guide* and the *Installation Guide*.

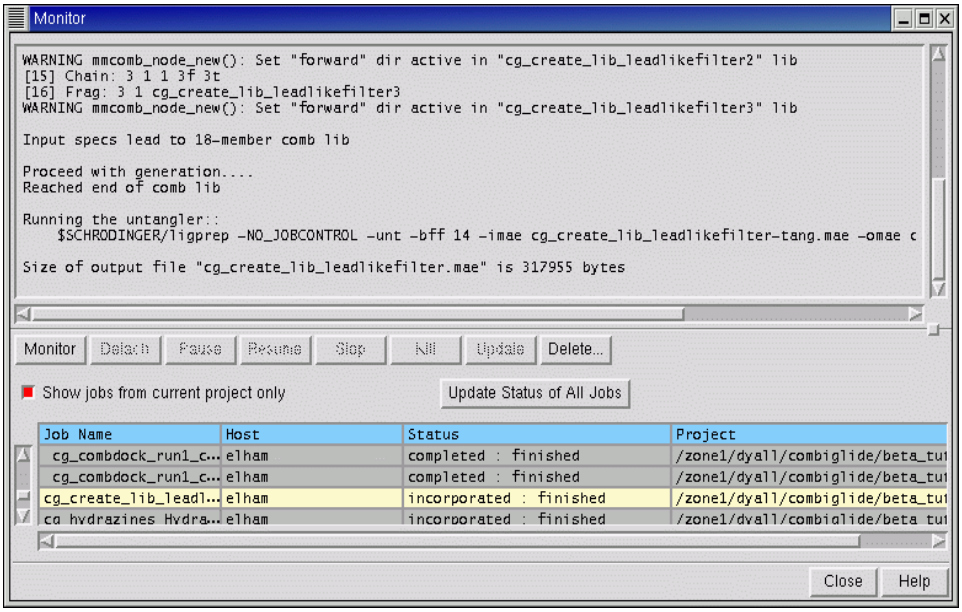

Figure 2.7. The* Monitor *panel.

2.11 Getting Help

Maestro comes with automatic, context-sensitive help (Auto-Help), Balloon Help (tooltips), an online help facility, and a user manual. To get help, follow the steps below:

- Check the Auto-Help text box at the bottom of the main window. If help is available for the task you are performing, it is automatically displayed there. It describes what actions are needed to perform the task.
- If your question concerns a GUI element, such as a button or option, there may be Balloon Help for the item. Pause the cursor over the element. If the Balloon Help does not appear, check that Show Balloon Help is selected in the Help menu of the main window. If there is Balloon Help for the element, it appears within a few seconds.
- If you do not find the help you need using either of the steps above, click the Help button in the lower right corner of the appropriate panel. The Help panel is displayed with a relevant help topic.
- For help with a concept or action not associated with a panel, open the Help panel from the Help menu or press CTRL+H.

If you do not find the information you need in the Maestro help system, check the following sources:

- The *Maestro User Manual*
- The Frequently Asked Questions page on the Schrödinger Support Center.

You can also contact Schrödinger by e-mail or phone for help:

- E-mail: help@schrodinger.com
- Phone: (503) 299-1150

2.12 Ending a Maestro Session

To end a Maestro session, choose Quit from the Maestro menu. To save a log file with a record of all operations performed in the current session, click Quit, save log file in the Quit panel. This information can be useful to Schrödinger support staff when responding to any problem you report.

Focused Library Design Tutorial

This chapter takes you through the use of CombiGlide for focused library design, including reagent preparation and combinatorial screening. The example used in this tutorial is a pyrazole library, which is designed to generate inhibitors of p38 MAP kinase. The synthetic approach for these compounds is described in Figure 3.1.

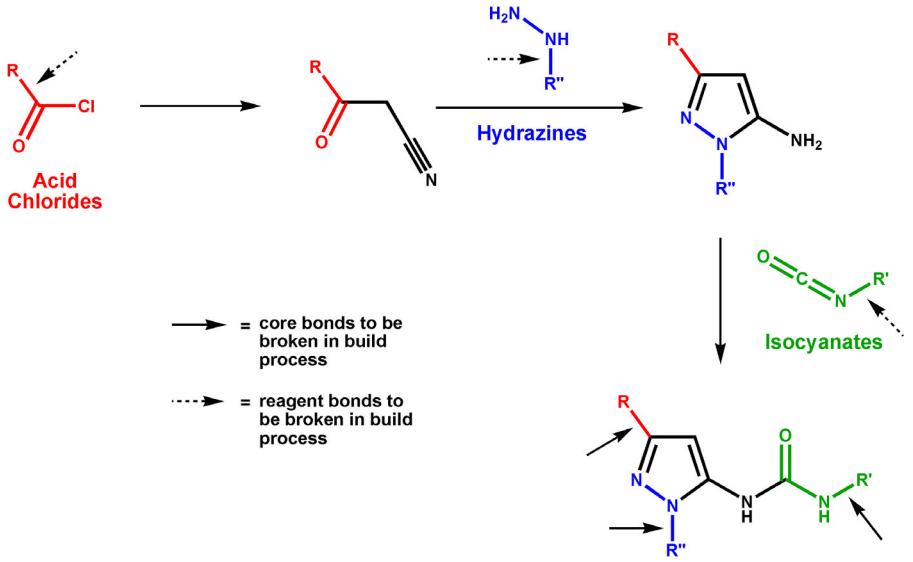

Figure 3.1. Synthetic route to pyrazole library.

The *core* is the structural element that is constant throughout the library. In the pyrazole example, the core is the structure given in Figure 3.2 minus the R, R', and R" groups.

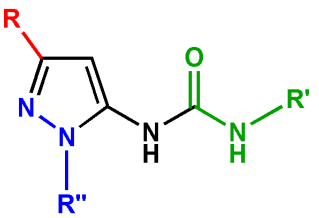

Figure 3.2. Core structure for pyrazole library design.

CombiGlide builds library members by adding the R, R', and R" groups from the reagents to the core structure. In the first part of the CombiGlide workflow, you provide a 3D, minimized structure of a molecule that contains this core, define the points at which the R, R', and R" groups are to be attached, and associate a set of reagents with each attachment point. You then select a receptor and set up parameters for docking with Glide. CombiGlide performs a series of docking calculations to determine a reduced set of reagents that is likely to contain the best candidates for the chosen receptor. In the final stage, you can narrow the library down to a small set, using various strategies for selection of the "best" reagents, then generate the library.

3.1 Preparing for the Exercises

To do the exercises, you must have access to an installed version of Maestro 7.5 and CombiGlide 1.0. For installation instructions, see the *Installation Guide*. Before you start Maestro, you must create a working directory, and copy files from the CombiGlide distribution into this directory.

To set up the working directory:

1. Set the `SCHRODINGER` environment variable to the directory in which Maestro and CombiGlide are installed:

   csh/tcsh: `setenv SCHRODINGER` *installation_path*

   sh/bash/ksh: `export SCHRODINGER=`*installation_path*

1. Change to a directory in which you have write permission.
2. Create a working directory for the tutorial:

   `mkdir` *workdir*

3. Change to the working directory:

   `cd` *workdir*

4. Copy all the files for the tutorial to this directory:

   `cp -r $SCHRODINGER/combiglide-v`*version*`/tutorial/* .`

   Here, *version* is the 5-digit version number of the CombiGlide distribution.

To start Maestro:

5. Start Maestro with the command:

   `$SCHRODINGER/maestro &`

   The Maestro main window is displayed.

6. Choose Save As from the Project menu and save your project as `cg_tutorial`.

   All the results are saved in the project, so you must save the project if you want to exit Maestro and resume the tutorial or view the results later.

3.2 Preparing the Reagents

The structures of the reagents that you want to use are often 2D structures. CombiGlide converts these structures to all-atom 3D structures suitable for the docking stage of the process, using LigPrep. The information needed to identify the fragment that will be added to the core is also added during reagent preparation. In this exercise, you will prepare the three reagent files needed to evaluate the pyrazole library.

1. Choose Reagent Preparation from the CombiGlide submenu of the Applications menu.

   The Reagent Preparation panel opens.

2. Click Browse, select `acid_chlorides.sdf` from your working directory, and click Open.

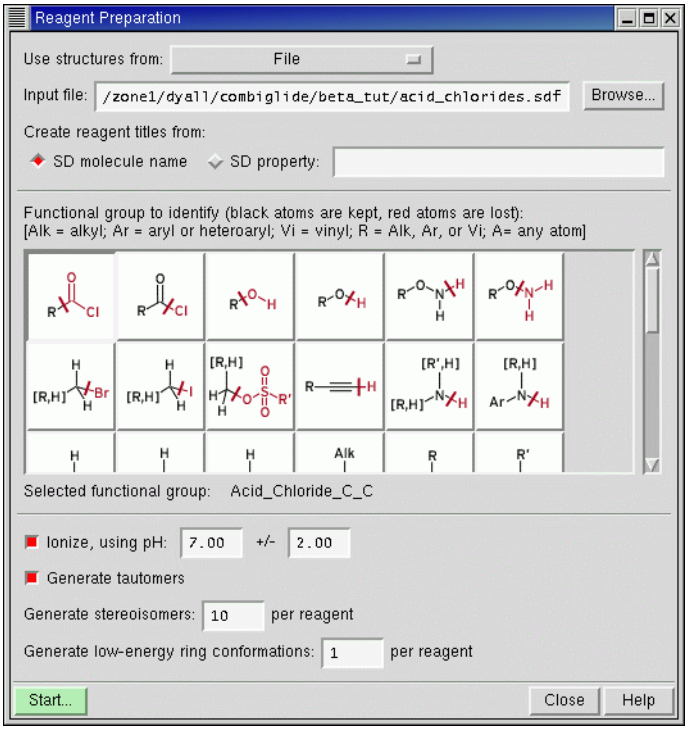

Figure 3.3. The Reagent Preparation panel.

3. Select SD property in the Create reagent titles from section and type `ReagentCode` into the text box.

   The ReagentCode property from the SD file will be used for the reagent title. Reagent titles are used for identification in CombiGlide, so it is important to set unique titles.

4. Click the Acid_Chloride_C_C button in the Functional group to identify section.

   Note that there is more than one copy of most functional groups. In each copy, a different bond is replaced during the build process. When you select a functional group, you are also selecting the bond that is replaced.

   The name of the button, displayed in the tooltip, encodes the functional group, the fragment that will be kept and the fragment that will be discarded in the build process. The name of the functional group is Acid_Chloride (acid chloride). The two C's at the end of the name define the atoms on either side of the bond that is replaced in the build process: the first is the atom in the fragment that is kept, and the second is the atom in the fragment that is discarded. In this case, the C atom of the –COCl group is discarded, and the C atom of the R group is kept. Thus, what is attached to the core is just the R group. For more information on the functional group definitions, see Section 4.2.2 of the *CombiGlide User Manual*.

5. Click Start.

   The Start dialog box opens. This dialog box allows you to adjust job settings, such as selecting a host and a job name. For this exercise, you can use the defaults.

6. Click Start in the Start dialog box.

   The Monitor panel opens automatically and shows the progress of the reagent preparation process. The job is finished when the Status changes to incorporated : finished.

   A number of files (`cg_acid_chlorides_Acid_Cl_C_C*`) are written to your working directory. The `cg_acid_chlorides_Acid_Cl_C_C.bld` file is the file used by CombiGlide in the build process. Do not delete any of the reagent preparation files since many of them are used later in CombiGlide.

7. Repeat the reagent preparation process (Step 2 – Step 6) for the other two reagent files:

   - With `hydrazines.sdf` use the Hydrazine_C_N functional group.
   - With `isocyanates.sdf`, use the Isocyanate_C_N functional group.

8. Close the Reagent Preparation panel.

You have now prepared all of the necessary reagent files. One of the reagents in the isocyanates input file contains an ionizable group and thus four structures are in the output file. The other two files should have three structures each. If you want to examine any of these files, you can import them into Maestro. When you open the Import panel, choose ReagentPrep from the Format option menu.

3.3 Importing the Core-Containing Molecule

To run CombiGlide, you must supply a molecule that contains the core structure. This molecule must be an all-atom, 3D structure that has a reasonable representation of the experimental geometry of the core structure. Ordinarily you would have to build or obtain this structure and minimize it using MacroModel or LigPrep, for example. For this tutorial, the core has already been built and minimized, and you only need to import it.

1. Click the Import structures button in the Maestro toolbar.

   

   The Import panel opens.

2. Ensure that Maestro is chosen from the Format option menu.

3. Select `core_tutorial.mae` and click Import.

   The 3D, minimized core-containing molecule is imported into the Project Table and displayed in the Workspace.

3.4 Defining the Reagent Combinations

Once you have a core-containing molecule and a set of reagents, you can start the combinatorial screening process. First, you must select the core-containing molecule, and determine which bonds in this structure will be replaced in the build process for each of the reagents. These are the *attachment positions*. In the pyrazole library example, the bonds to be replaced are marked in Figure 3.5.

1. Choose Combinatorial Screening from the CombiGlide submenu of the Applications menu.

   The Combinatorial Screening panel opens with the Define Combinations step displayed and Pick Molecule selected.

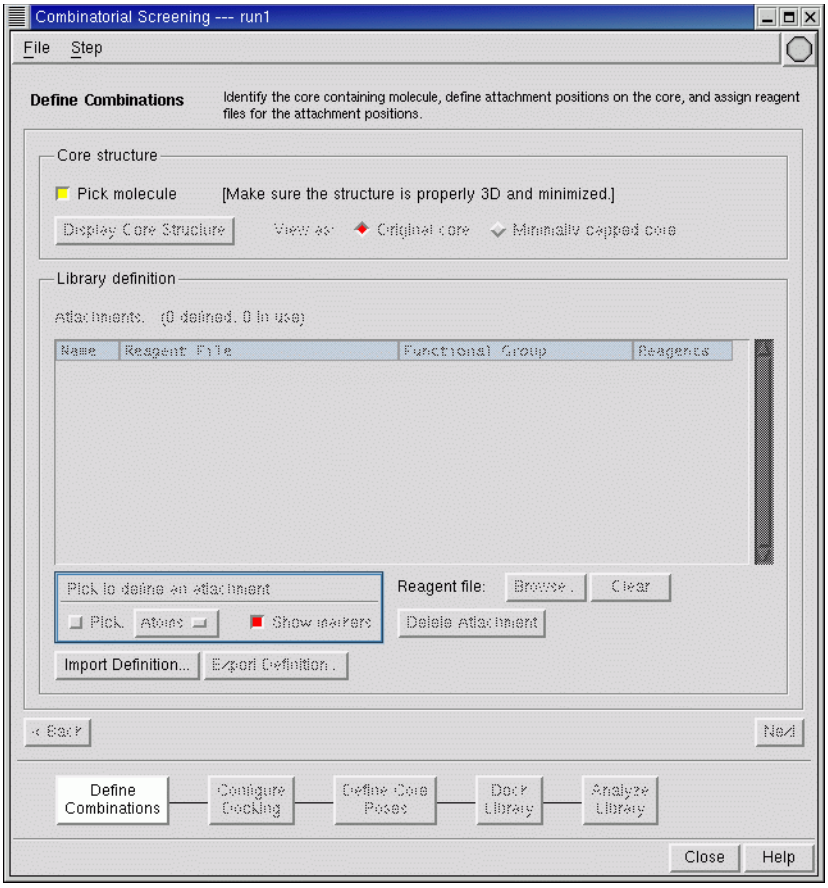

Figure 3.4. Define Combinations step, initial view.

2. Pick any atom in the core-containing molecule, which is displayed in the Workspace.

   The Core Molecule Title dialog box is displayed.

3. Type in a title and click OK.

The core-containing molecule is now defined. Next, you will define the attachment positions by clicking on the atoms of the bonds to be replaced in the build process. The bonds to be replaced are designated by numbers in Figure 3.5.

4. For the acid chloride bond, pick atom 1 then pick atom 2.

   A magenta cube appears around atom 1 when you pick it. After picking atom 2, a turquoise arrow pointing from atom 1 to atom 2 is displayed, labeled with the attachment position name, which is a number by default. The Select Reagent File panel opens.

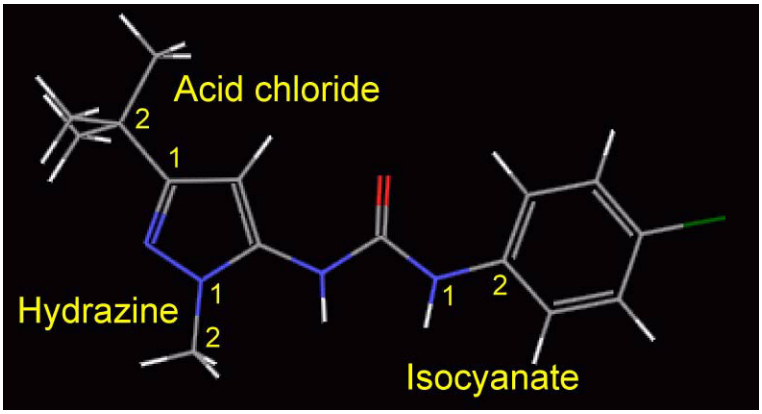

Figure 3.5. Attachment positions for the three reagents.

5. Select the *reagent*`.bld` file to be associated with this attachment position and click OK.

   For the acid chloride position, this file is `cg_acid_chlorides_Acid_Cl_C_C.bld`.

   The attachment position and the reagent file name appear in the Attachments table along with the name of the functional group used to prepare the reagent file and the number of reagents in the file. (If multiple stereoisomers, ionization states, and tautomeric states were generated from the same molecule during reagent preparation, all of them are considered the same reagent and only counted once.)

   The arrow over the bond that will be replaced changes to a tube connecting to a sphere, colored gold, with the name associated with the position in the Attachments table still displayed. You can change the name of the attachment by editing the table cell.

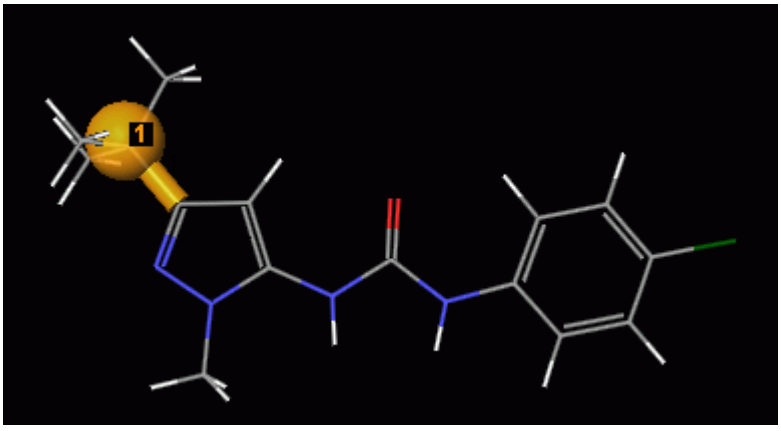

Figure 3.6. Attachment position for the acid chlorides after adding reagent file.

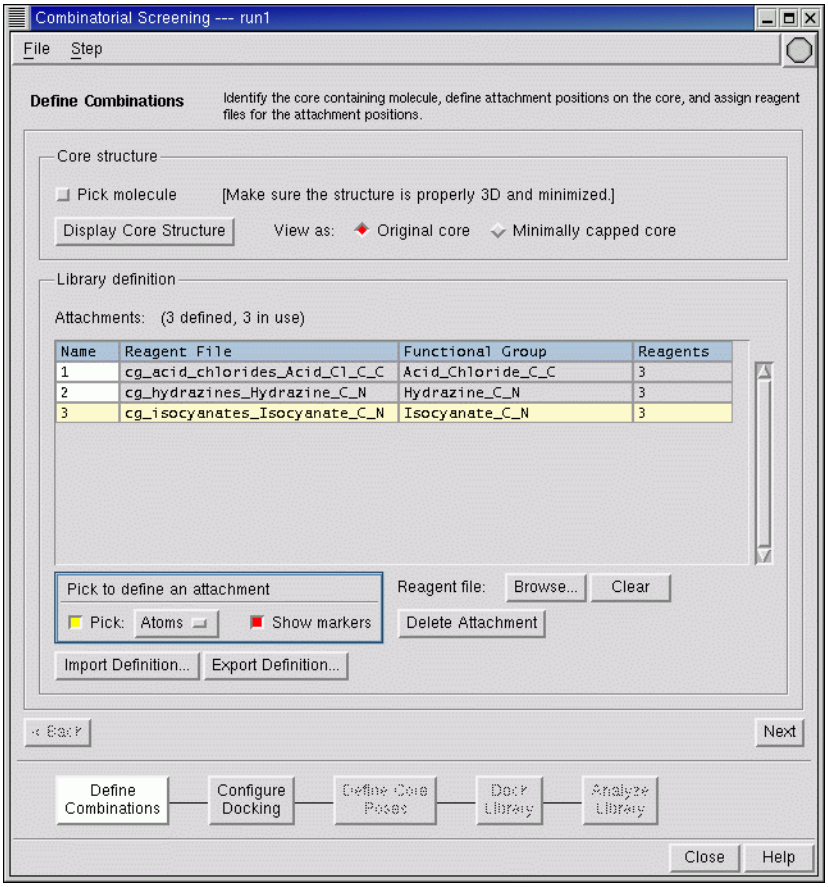

Figure 3.7. Define Combinations step after defining attachment positions.

6. Repeat the above process (Step 4 and Step 5) to define the attachments for the hydrazine and isocyanate positions.

   If you make a mistake in the attachment position, select the table row and click Delete Attachment. You can then pick the correct atoms for the attachment position. If you make a mistake in the reagent file selection, select the table row and click Browse. You can then select the correct reagent file. When you select a table row, the attachment position is marked in turquoise in the Workspace.

7. Click Next.

   The Configure Docking step is displayed.

3.5 Configuring the Glide Docking Calculations

The next step is to configure the CombiGlide docking calculations. In a real application, you would select a receptor and generate the grids before starting the combinatorial screening process. You would then set up the parameters for the docking process in this step. For this tutorial, grids have already been generated.

1. Click Browse.
2. Navigate to the `receptor_grids` directory, select `receptor_grid.grd`, and click OK.

   The path to the grid files is displayed in the Receptor grid base name text box. We will be using the default docking settings in the tutorial, so no further settings need to be made.

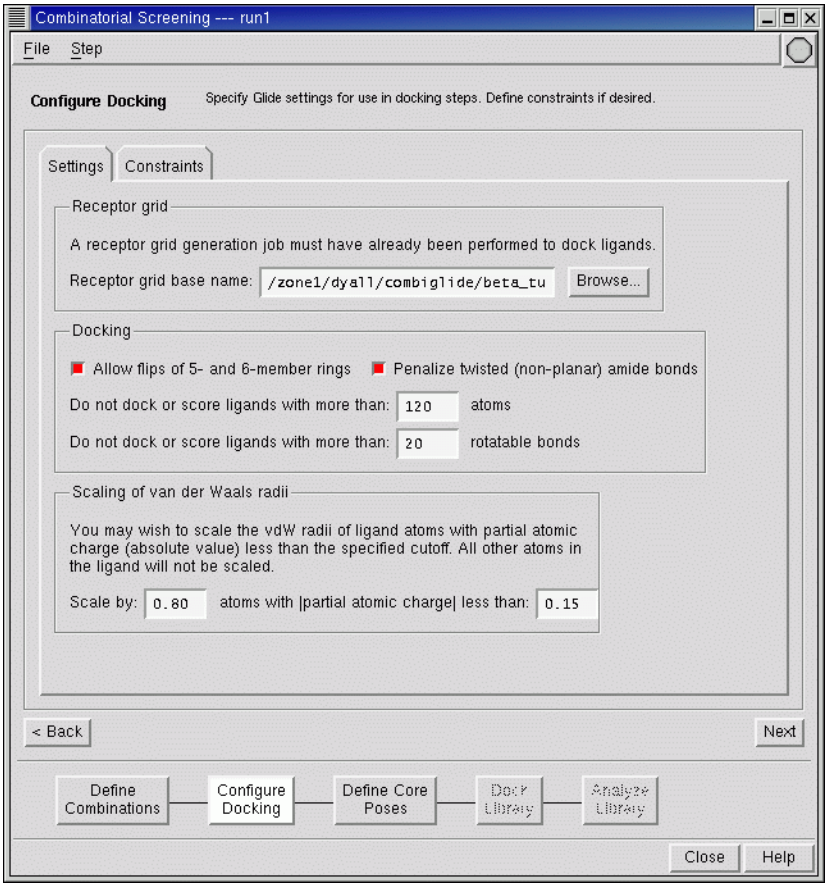

Figure 3.8. Configure Docking step after selecting grid file.

As with normal Glide jobs, the grid files must reside in a location that is accessible to the host on which the docking jobs will be run. For example, if your docking jobs will be run on a cluster, the grid files must be in a directory mounted on the compute nodes of the cluster.

3. Click Next.

   The Define Core Poses step is displayed.

3.6 Defining the Core Poses

In the tutorial, you will use the default settings for the docking of the core-containing molecule. The poses of the core-containing molecule are used as initial poses in the library docking.

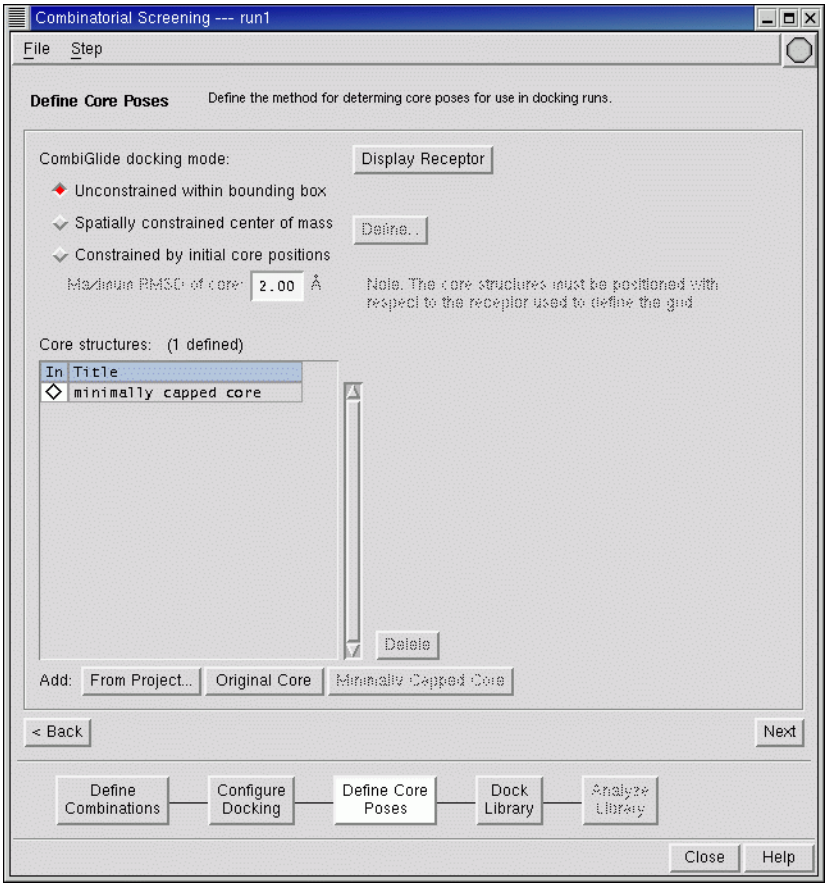

Figure 3.9. Define Core Poses step.

The structure to be used in the core pose determination is the *minimally capped core*, which should appear automatically in the Core structures table. The minimally capped core is the core molecule with the minimal capping group at each attachment position. The minimal capping group is defined on page 50 of the *CombiGlide User Manual*. You can view the minimally capped core by clicking the diamond in the In column for the minimally capped core in the Core structures table. You can also view the receptor by clicking the Display Receptor button.

- Click Next.

  The Dock Library step is displayed.

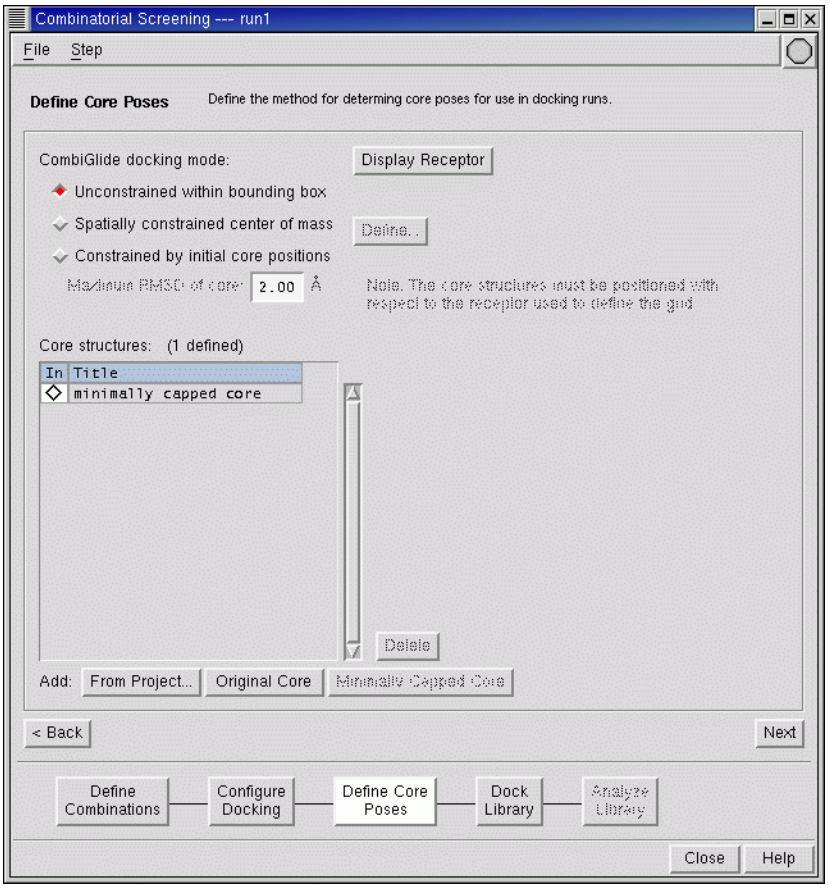

Figure 3.10. Dock Library step, initial view.

3.7 Docking the Structures

You are now ready to start the docking phase of CombiGlide. In this phase, all possible structures generated by a single substitution at each attachment position are docked first ("single-position docking"), then a selection process is run on the results of this docking run to screen out poor poses, and finally a set of fully substituted structures is built and docked.

1. Enter 32 in the Maximum number of combinatorial structures to dock text box.

   In the final stage of docking, CombiGlide will build and dock the structures that the selection algorithm considers to be the best, up to a maximum of 32 structures. The total number of structures that can be generated from the 3x3x3 library is 3x3x4 = 36 since one of the reagent files contained an ionizable group and therefore now contains four structures.

2. Click Combinatorial.

   The Start dialog box opens.

   This choice runs the entire docking process: single-position docking, selection, and all-position docking. If you wish to view the results of the single-position docking runs before proceeding to docking the fully substituted structures, click Single Positions instead of Combinatorial. Once the single-position results are returned, you can perform the all-position docking by clicking Combinatorial.

3. Select the host you wish to run the docking jobs on and distribute them as you see fit.

   For the tutorial, it is not necessary to separate the docking into subjobs since you are evaluating a small library. The overall docking process will take approximately 5-6 hours on a 2 GHz processor.

4. Click Start.

   The jobs start and the octagon button turns green and starts spinning, but the Monitor panel does not open. You can open the Monitor panel to monitor the docking jobs during the CombiGlide run by clicking the octagon button.

   When all the jobs finish, the # Single and # Comb columns are populated in the Reagent retention table, and the total number of final docked structures is reported in the Number of final structures text box in the Combinatorial results section. # Single is the number of reagents at the given position in the structures that were successfully docked in the single-position docking stage. # Comb is the number of reagents at the given position in the structures that were successfully docked in the all-position docking stage. There should be 3 reagents in each column for each position.

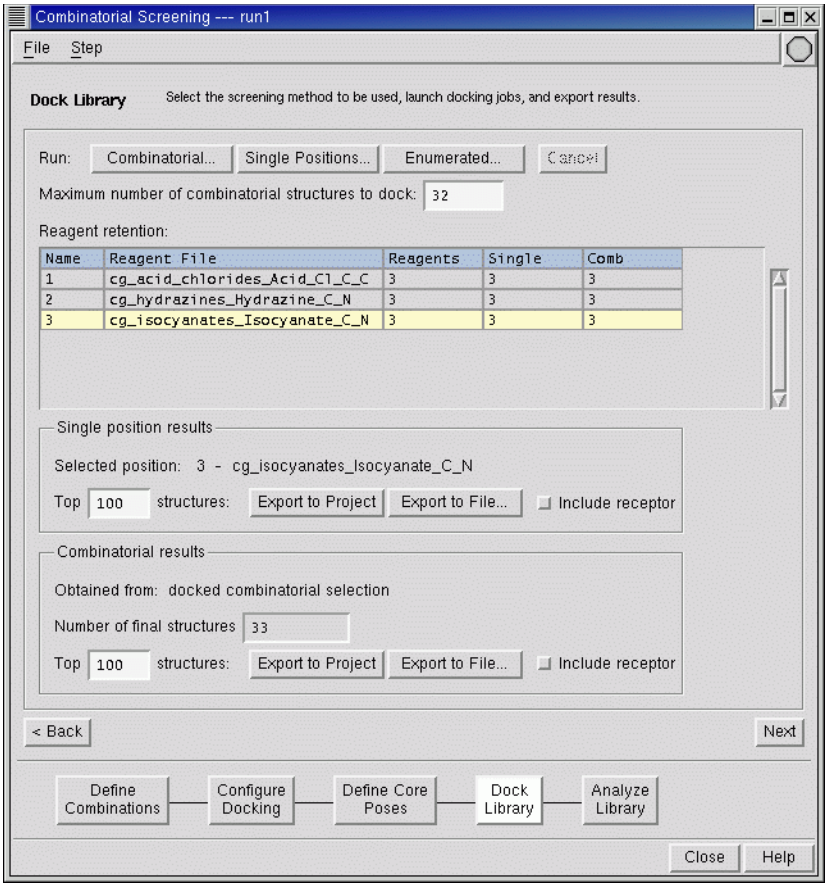

Figure 3.11. The Dock Library step after docking.

You can view the single-position results by selecting the row for the attachment position you wish to view in the Reagent retention table, then clicking Export to Project in the Single position results section of the panel. You can then view the structures using the Project Table. Note that more than one pose is saved for each reagent.

To view the combinatorial results, click Export to Project in the Combinatorial results section. You can then view the structures using the Project Table.

5. Click Next.

   The Analyze Library step is displayed.

3.8 Analyzing the Library

When the docking jobs are finished, you can proceed to design the optimal focused combinatorial library based on the all-position docking results.

1. Click Filter and Select.

   The Filter and Select dialog box opens.

2. In the Selection Strategy folder, select Combinatorial and GlideScore.

3. Enter 24 into the Maximum library size text box.

4. Click OK.

   CombiGlide calculates the optimal combinatorial library using the GlideScore to determine the best reagents, with a maximum library size of 24. As can be seen in the #Lib column of the uppermost table in the panel, a 3x3x2 library (18 members) was generated.

5. Click on the row for the attachment position associated with the isocyanate reagent file (Reagent Title: cg_isocyanates_Isocyanate_C_N).

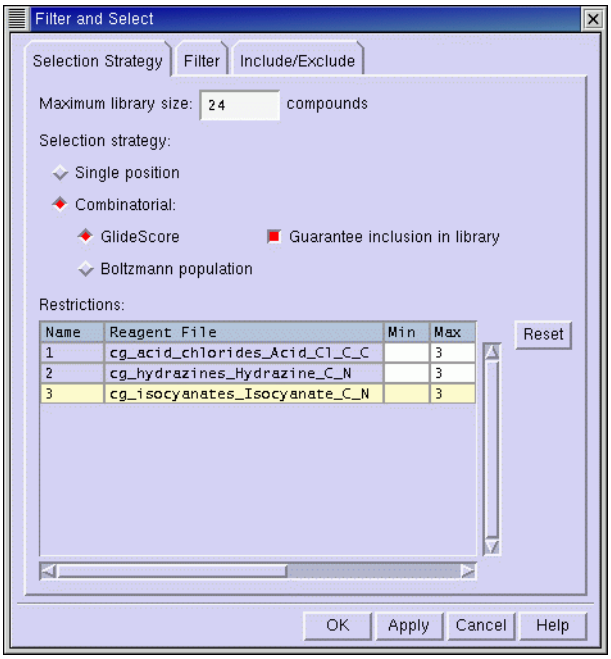

Figure 3.12. The Selection Strategy folder of the Filter and Select dialog box.

The data for this attachment position appears in the Reagents table. The rank 1 reagent is the reagent at that position for the best scoring structure from the all-position docking. The row for the rank 3 reagent is colored blue to indicate that the reagent was not selected for the library but was the reagent from the next best scoring structure from the all-position docking. This feature allows you to see the reagents that were close to being included in the focused library, and thus can help you to refine the library.

To view the docked pose of the best-scoring structure containing a particular side chain, click on the diamond to the left of the reagent in the Reagents table.

6. Save the results of this library selection strategy by clicking Save and giving it the name `original`.

Next, you will filter the library using a set of properties, to further refine the library.

7. Click Filter and Select.
8. In the Filter folder, select Leadlike from the Filter set option menu.
9. Click OK.

   This strategy adds a filter to the previous strategy, and returns a 2x3x3 library.

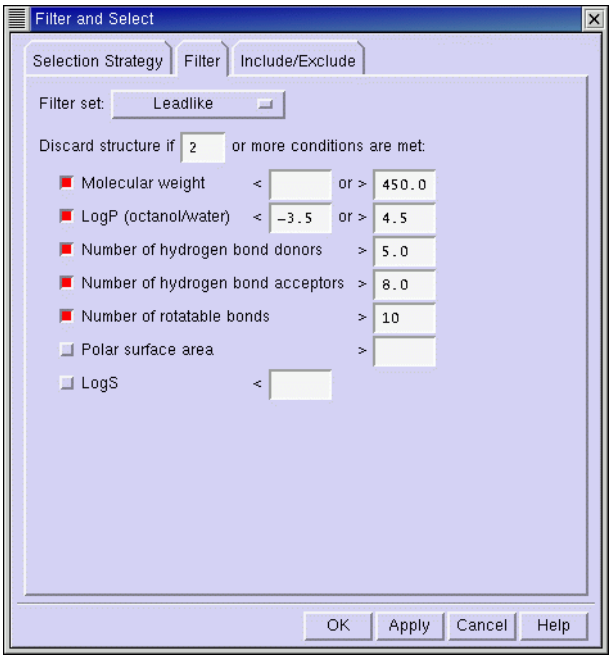

Figure 3.13. The Filter folder of the Filter and Select dialog box.

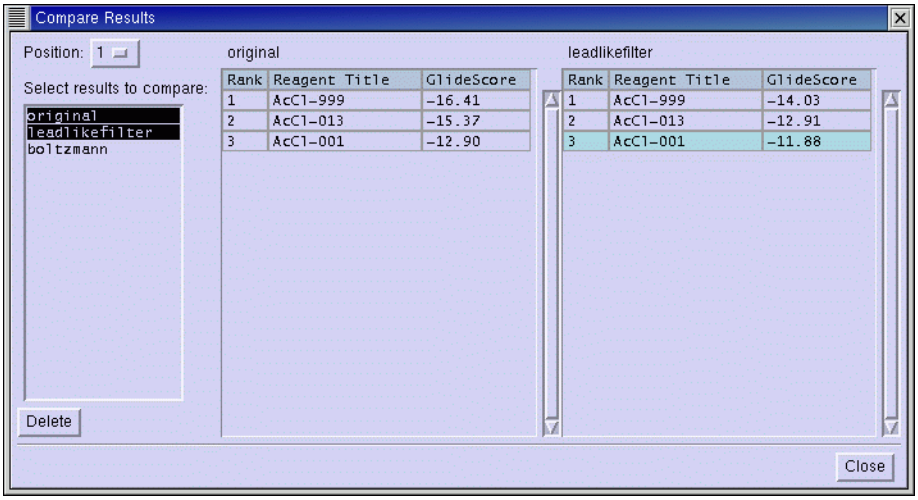

Figure 3.14. The Compare Results dialog box.

10. Save the results of this library selection strategy by clicking Save and giving it the name `leadlikefilter`.

To compare results from different strategies:

11. Click Compare in the Results section.

    The Compare Results dialog box opens.

12. Select original and leadlikefilter from the Select results to compare list.

13. Select 3 from the Position option menu.

    The reagents selected with both strategies appear side-by-side for comparison.

To generate a text file summarizing the results of the current strategy, click Write Text File in the Results section of the Analyze Library step. The file contains the settings used in the strategy, the GlideScore ranges, and the list of reagents selected for each attachment position.

Once you select your final focused library, you can enumerate the entire library that can be prepared from the reagents chosen by your selection strategy, by clicking Create Library. By default, the structures in the library are untangled and minimized.

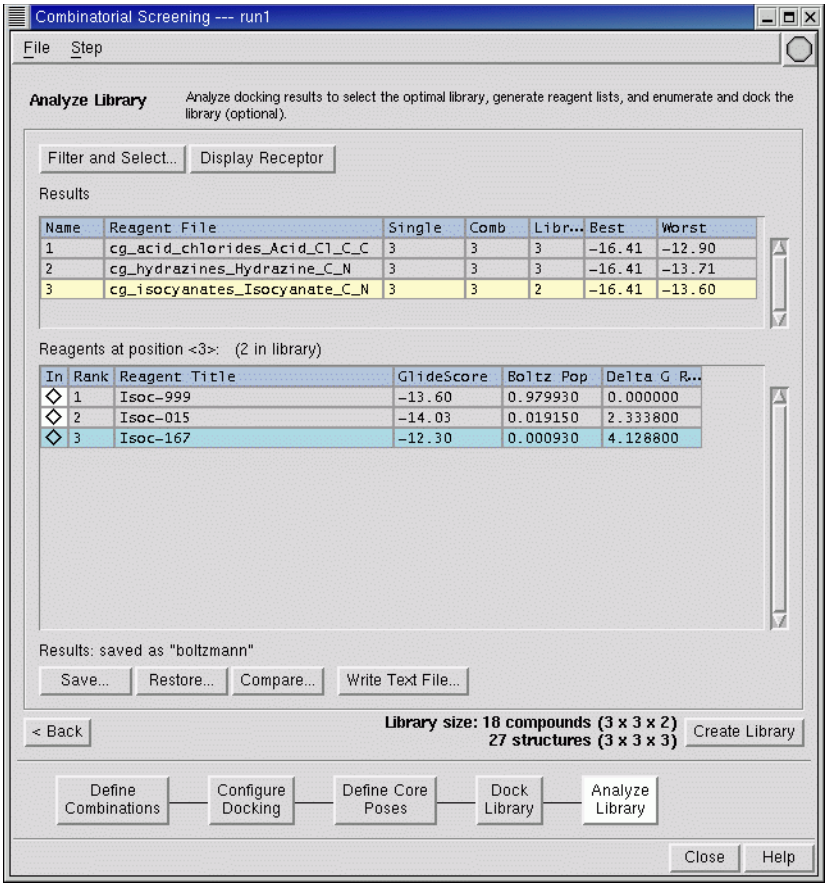

Figure 3.15. The Analyze Library step after analysis.

Getting Help

Schrödinger software is distributed with documentation in PDF format. If the documentation is not installed in `$SCHRODINGER/docs` on a computer that you have access to, you should install it or ask your system administrator to install it.

For help installing and setting up licenses for Schrödinger software and installing documentation, see the *Installation Guide*. For information on running jobs, see the *Job Control Guide*.

Maestro has automatic, context-sensitive help (Auto-Help and Balloon Help, or tooltips), and an online help system. To get help, follow the steps below.

- Check the Auto-Help text box, which is located at the foot of the main window. If help is available for the task you are performing, it is automatically displayed there. Auto-Help contains a single line of information. For more detailed information, use the online help.
- If you want information about a GUI element, such as a button or option, there may be Balloon Help for the item. Pause the cursor over the element. If the Balloon Help does not appear, check that Show Balloon Help is selected in the Help menu of the main window. If there is Balloon Help for the element, it appears within a few seconds.
- For information about a panel or the tab that is displayed in a panel, click the Help button in the panel. The Help panel is opened and a relevant help topic is displayed.
- For other information in the online help, open the Help panel and locate the topic by searching or by category. You can open the Help panel by choosing Help from the Help menu on the main menu bar or by pressing CTRL+H.

  To view a list of all available CombiGlide–related help topics, choose CombiGlide from the Categories menu in the Categories tab. Double-click a topic title to view the topic.

If you do not find the information you need in the Maestro help system, check the following sources:

- *Maestro User Manual*, for detailed information on using Maestro
- *Maestro Command Reference Manual*, for information on Maestro commands
- *CombiGlide User Manual*, for detailed information on using CombiGlide
- *Glide User Manual*, for detailed information on using Glide
- *Glide Quick Start Guide*, for Glide tutorials
- Frequently Asked Questions pages, at https://www.schrodinger.com/CombiGlide_FAQ.html

The manuals are also available in PDF format from the Schrödinger Support Center. Information on additions and corrections to the manuals is available from this web page.

If you have questions that are not answered from any of the above sources, contact Schrödinger using the information below.

E-mail: help@schrodinger.com
USPS: 101 SW Main Street, Suite 1300, Portland, OR 97204
Phone: (503) 299-1150
Fax: (503) 299-4532
WWW: http://www.schrodinger.com
FTP: ftp://ftp.schrodinger.com

Generally, e-mail correspondence is best because you can send machine output, if necessary. When sending e-mail messages, please include the following information, most of which can be obtained by entering `$SCHRODINGER/machid` at a command prompt:

- All relevant user input and machine output
- CombiGlide purchaser (company, research institution, or individual)
- Primary CombiGlide user
- Computer platform type
- Operating system with version number
- CombiGlide version number
- Maestro version number
- mmshare version number

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